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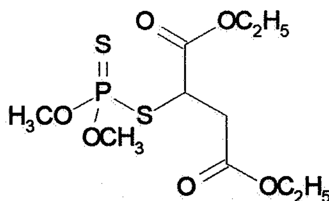
MALATHION



Shaughnessy No. 057701; Case 0248

(CBRS No. 11316; DP Barcode D187715)

Task 4

REGISTRANT'S RESPONSE TO RESIDUE CHEMISTRY DATA REQUIREMENTS

BACKGROUND

A/S Cheminova, through its authorized representatives (Jellinek, Schwartz, & Connolly, Inc.), has submitted a goat metabolism study (1992; 42581401) in response to the Malathion Reregistration Standard Guidance Document, dated 2/88. The study is reviewed herein for its adequacy in fulfilling data requirements under Guideline Reference No. 171-4 (b).

The qualitative nature of malathion residues in alfalfa, lettuce, cotton and wheat is adequately understood. The requirement for a poultry metabolism study remains outstanding.

Tolerances for malathion residues in/on food commodities are expressed in terms of *O,O*-dimethyl dithiophosphate of diethyl mercaptosuccinate [40 CFR §180.111, 40 CFR §185.3850, and 40 CFR §185.7000]. The HED Metabolism Committee has determined that the parent compound malathion and the metabolite malaoxon are the compounds that need to be regulated in/on plant commodities. Codex MRLs exist for residues of malathion *per se* in/on various plant and processed commodities. The Codex MRLs and the U.S. tolerances will be incompatible when the U.S. tolerance expression for plant commodities is revised to include both residues of malathion and the metabolite malaoxon.

The Pesticide Analytical Manual (PAM) Vol. II lists a TLC method, a GLC method with KCl thermionic detection, and a spectrophotometric method as Methods I, II, and III, respectively, for the enforcement of malathion tolerances. The Residue Chemistry Science Chapter of the Malathion Reregistration Standard, dated 7/87, recommends use of the GLC method for tolerance enforcement.

The Conclusions and Recommendations stated in this document pertain only to the nature of malathion residues in goats. Other residue chemistry data requirements specified in the Guidance Document are not addressed herein.

MALATHION.005

CONCLUSIONS AND RECOMMENDATIONS

1. The qualitative nature of malathion residue in lactating goats is adequately understood. The study indicates that following dosing of goats with [2,3-^{14}C]malathion at 115 ppm (1.6x the maximum theoretical dietary dose) in the diet for five consecutive days, the levels of total radioactive residues reached maximums of 2.79 ppm in milk, 2.28 ppm in liver, 2.21 ppm in kidney, 0.39 ppm in heart, 0.36 ppm in muscle, and 1.59 ppm in fat.

2. The study successfully identified majority of the radioactivity in the following goat matrices: milk (≥93% TRR), liver (83% TRR), kidney (78% TRR), heart (77% TRR), muscle (≥94% TRR), and fat (≥70% TRR). The principal ^{14}C-residues identified were triglycerides, fatty acids, tricarboxylic acids, lactose, and/or unspecified proteins. Malathion, the parent compound was not identified in any matrix. The only immediate malathion metabolites identified were malathion monocarboxylic acid and malathion dicarboxylic acid which were present in milk, kidney, and muscle in insignificant amounts.

3. The goat metabolism study is supported by acceptable storage stability data.

4. No method validation in meat and milk is required since no residues of concern were observed in these commodities (See conclusion 5 below).

5. Since neither malathion nor malaoxon (the residues of concern) were observed in meat or milk in the subject metabolism study, there is no need for tolerances in these commodities based on any dietary exposure to malathion residues. The present 4 and 0.5 ppm tolerances for malathion in meat and milk respectively involve direct animal treatments which would, in all probability, result in significant malathion residues of concern in these commodities. Therefore, if the direct animal treatment uses of malathion to cattle are canceled, then the present tolerances for meat and milk may be revoked. If the direct livestock treatment use is supported, appropriate dermal metabolism and magnitude of the residue studies are required.

The molecular structures of malathion and its immediate metabolites that were identified in goat matrices are presented in Table 1.

Table 1. Malathion and its immediate metabolites in lactating goats.

Code	Chemical Name / Structure	Substrate	MRID	Common Name
I.	O,O-dimethyl dithiophosphate of diethyl mercaptosuccinate			**malathion**
II.	O,O-dimethyl dithiophosphate of mercaptosuccinic acid	goat kidney and muscle	42581401[a]	**malathion dicarboxylic acid; DCA**
III.	O,O-dimethyl dithiophosphate of ethyl mercaptosuccinate	goat milk and kidney	42581401[a]	**malathion monocarboxylic acid; MCA**

[a] Identification confirmed by a second method.

DETAILED CONSIDERATIONS

Qualitative Nature of the Residue in Lactating Goats

In-life Phase

A/S Cheminova submitted data (1992; MRID 42538901) depicting the metabolism of [2,3-^{14}C]malathion in lactating goats. The biological portion of the study was conducted by Bio-Life Associates, Ltd. (Neillsville, WI). Two lactating goats were orally dosed with [2,3-^{14}C]malathion, via gelatin capsule filled with cornstarch, once daily for five consecutive days at 115 ppm, based on a feed intake of 1.5 kg/goat/day. The malathion test material had a specific activity of 9.8 μCi/mg (21,756 dpm/μg) and a radiochemical purity of 96.4%. A control goat received a capsule containing only cornstarch.

During the study, the base diet consisted of commercial goat feed and clover-prairie hay; water was provided *ad libitum*. Calculations deriving the daily dose of malathion as well as information pertaining to feed consumption, milk production, and general health of the test animals were provided. Urine, feces, and milk were collected from each goat one day prior to treatment and each day during treatment. Each goat was sacrificed ca. 24 hours following the final dose. Kidney, liver, heart, muscle, fat, and rumen contents were collected at sacrifice period. All samples were immediately frozen after sampling, shipped frozen on dry ice to the analytical laboratory (Midwest Research Institute, Kansas, MO), and stored at ca. -10 C until analysis. Final analyses were conducted within ca. six months of sample collection.

Based on a goat diet consisting of 50% alfalfa hay, 25% corn grain, and 25% sugar beet molasses (having malathion tolerances of 135 ppm, 8 ppm, and 1 ppm, respectively), the maximum daily dietary intake of malathion residues by goats is ca. 70 ppm. Therefore, the amount of malathion administered to the test goats is ca. 1.6x the maximum daily dietary burden. This dietary burden estimate was based on a diet which may not be realistic for goats. Nevertheless, this is one of many possible diets which represent the maximum theoretical dietary consumption.

Total radioactive residues (TRR)

Subsamples of the goat tissues (except fat) were homogenized in four volumes of 10% ethanol in water and analyzed in duplicate for radioactivity by liquid scintillation spectrometry (LSS) following combustion. The TRR in milk was directly determined by LSS. The detection limit for TRR determinations was <0.01 ppm. The registrant provided all equations used to calculate ppm equivalents. The TRR found in tissues and milk of dairy goats are presented in Table 2. Table 2 indicates that radioactive residues were found in/on the milk and all tissues of test goats. The average amount of radioactivity was lowest in muscle (ca. 0.2 ppm) and heart (ca. 0.4 ppm) tissues. The radioactivity in milk and the remainder of tissues ranged from 0.94 to 2.46 ppm.

Table 2. Total radioactive residues in milk and tissues from lactating goats dosed with [2,3-^{14}C]malathion at 115 ppm (1.6x) for five consecutive days.

Matrix		TRR, ppm [2,3-^{14}C]malathion equivalents [a]		
		Goat 1	Goat 2	Average of 2 Goats
Milk:	Day-1 [b]	<0.01	<0.01	<0.01
	Day-1	1.49	1.35	1.42
	Day-2	1.93	2.14	2.04
	Day-3	1.98	2.19	2.08
	Day-4	2.14	2.79	2.46
	Day-5	2.03	2.26	2.14
Liver		2.28	2.23	2.26
Kidney		2.21	1.71	1.96
Heart		0.39	0.37	0.38
Muscle (semimembranous)		0.26	0.23	0.24
Muscle (longissimus dorsi)		0.36	0.19	0.28
Fat (omental)		1.59	0.40	1.00
Fat (back)		1.39	0.50	0.94
Fat (perirenal)		1.31	0.75	1.03

[a] Mean of duplicate analyses.
[b] Sample was collected one day prior to the administration of the first dose.

Extraction and hydrolysis of residues

The milk and tissue samples were subjected to two slightly different sets of fractionation procedures to determine the distribution of radioactive residues. The first set of procedures (referred by the registrant as solvent extraction studies) was to determine which solvents and hydrolysis procedures were suitable for extracting radioactive residues; the fractions from the first procedures were not used for metabolite identification. The second set of procedures was a refinement of the first, and the resulting fractions were used for metabolite identification. At each step of the procedure, aliquots or subsamples were analyzed for radioactivity by LSS or combustion/LSS. Both procedures are briefly described below.

In the first fractionation scheme, aliquots of milk were extracted once with hexane and centrifuged. The remaining milk sample was re-extracted twice with diethyl ether and centrifuged. The ether phases were combined and mixed with sodium sulfate. The ether was decanted and the sodium sulfate was washed three times with diethyl ether. The ether phases were combined and concentrated by evaporation. The sodium sulfate was dissolved in water. The residual solids were further subjected to sequential treatments of methanol:TFA, 0.2 N ammonium hydroxide, hydrochloric acid, and 3 N sodium hydroxide. Tissue samples were homogenized in 1% TFA in diethyl ether, and centrifuged. The organic phase was decanted, the solids were re-extracted with 1% TFA in ether, and the ether extracts were combined. The residual tissue solids were further subjected to sequential treatments of 1% TFA in methanol, 0.2 N ammonium hydroxide, and 3 N sodium hydroxide. The registrant provided extensive data showing the distribution of radioactive residues as a result of the schemes described above. The procedures recovered 96-111% of TRR in milk and 92-142% of TRR in tissues. The methanol:TFA fraction accounted for majority (67-75% TRR) of the extractable residues in milk. The radioactivity in tissues was broadly distributed among polar and nonpolar solvents. It should be re-emphasized that fractions from these procedures were not used for metabolite identification.

In the second fractionation scheme, milk and tissue subsamples were homogenized twice with 0.1% TFA in diethyl ether and centrifuged. The ether supernatants were combined and the supernatants were

evaporated to dryness and redissolved in tetrahydrofuran. The residual solids were extracted with 1% TFA in methanol and the extract was evaporated to dryness. The dried residues were redissolved in 2% TFA containing acetonitrile and water, and then filtered. The unextracted residues were hydrolyzed in 3 N sodium hydroxide at ca. 90 C for one hour, adjusted to pH 3 by the addition of acid, and centrifuged. The supernatant was lyophilized and the lyophilized residues were redissolved in water, centrifuged, and filtered. The precipitates formed after addition of acid to the basic hydrolysate, were hydrolyzed with Protease Type XXV (pronase); enzyme hydrolysis was terminated by adjustment to <pH 3 with trichloroacetic acid. Following centrifugation, the supernatant was decanted, filtered and lyophilized.

The distribution of ^{14}C-activity in extracts of milk and tissues us summarized in Tables 3 and 4. In milk, the methanol (50-60% TRR) and ether (21-31% TRR) extracts contained the majority of the radioactivity. In tissues, radioactivity was broadly distributed among the various fractions.

Milk was further analyzed to determine the amount of radioactivity which can be incorporated into fat, whey, and casein. Aliquots of day-5 milk (2.75 ppm TRR) were centrifuged for one hour at 4 C which resulted in the formation of an upper layer of milk fat. The milk fat was removed after solidification by cooling to ca. 0 C. Following removal of fat layer, the sample was further centrifuged. The liquid portion (whey) was collected and adjusted to ca. pH 4.5 with 20% formic acid to precipitate casein. The sample was then heated at 30 C for 30 minutes, after which the heated sample was added to the solids remaining after the initial centrifugation. The distribution of radioactivity following these procedures was: fat (0.48 ppm, 17.4% TRR), whey (1.38 ppm, 50.1% TRR), and dry casein (0.66 ppm, 24.1% TRR).

Table 3. Distribution of total radioactive residues (TRR) in milk from lactating goats dosed with [2,3-^{14}C]malathion at 115 ppm (1.6x) for five consecutive days.

Substrate	Fraction	Malathion equivalents		Characterization/Identification [a]
		% TRR	ppm	
Milk Day 1 (1.49 ppm [b]; Goat No. 1)	Et_2O:TFA	20.5	0.31	Lactose (1.05 ppm, 70.5% TRR), triglyceride (0.25 ppm, 16.8% TRR), and protein (0.09 ppm, 6.0% TRR) were identified [c] in various fractions.
	MeOH:TFA	49.7	0.74	
	3 N NaOH	12.6	0.19	
	Enzyme	0.02	0.19	Total identified = 1.39 ppm, 93.3% TRR
	Non-extractable	0.7	0.01	Not further analyzed.
Day-3 Milk (2.66 ppm [b]; Goat No. 2)	Et_2O:TFA	30.9	0.82	Lactose (1.56 ppm, 58.6% TRR), triglyceride (0.52 ppm, 19.5% TRR), protein (0.11 ppm, 4.1% TRR), and MCA (0.01 ppm) were identified in various fractions.
	MeOH:TFA	60.4	1.61	
	3 N NaOH	11.7	0.31	
	Enzyme	--	--	Total identified = 2.20 ppm, 82.2% TRR
	Non-extractable	--	--	

[a] Data were obtained from registrant's summary tables. The summary data do not specify the metabolites nor the amounts identified per fraction.
[b] TRR values were re-determined prior to characterization/identification of residues.
[c] Identifications were made by a combination of reverse-phase HPLC, anion exchange HPLC, and gel permeation chromatography.

Table 4. Distribution of total radioactive residues (TRR) in tissues from lactating goats dosed with [2,3-^{14}C]malathion at 115 ppm (1.6x) for five consecutive days.

Substrate	Fraction	Malathion equivalents		Characterization/Identification [a]
		% TRR	ppm	
Liver (2.21 ppm [b]; Goat No. 2)	Et_2O:TFA	9.3	0.21	Protein (0.87 ppm, 39.0% TRR), pyruvic acid (0.62 ppm, 27.8% TRR); lactic acid (0.13 ppm, 5.8% TRR), oleic acid (0.10 ppm, 4.5% TRR), triglyceride (0.07 ppm, 3.1% TRR), fumaric acid (0.04 ppm, 1.8% TRR), and stearic acid (0.03 ppm, 1.3% TRR) were identified [c] in various fractions. Total identified = 1.86 ppm, 83.3% TRR
	MeOH:TFA	18.3	0.40	
	3 N NaOH	35.0	0.77	
	Enzyme	1.9	0.04	
	Non-extractable	7.0	0.15	Not further analyzed.
Kidney (1.71 ppm [b]; Goat No. 2)	Et_2O:TFA	10.2	0.18	Protein (0.79 ppm, 46.2% TRR), lactic acid (0.16 ppm, 9.4% TRR), pyruvic acid (0.14 ppm, 8.2% TRR), triglyceride (0.10 ppm, 5.8% TRR), DCA (0.06 ppm, 3.5% TRR), fumaric acid (0.04 ppm, 2.3% TRR), oleic acid (0.03 ppm, 1.8% TRR), and MCA (0.01 ppm, 0.6% TRR) were identified in various fractions. Total identified = 1.33 ppm, 77.8% TRR
	MeOH:TFA	15.8	0.28	
	3 N NaOH	34.5	0.61	
	Enzyme	6.2	0.11	
	Non-extractable	7.9	0.14	Not further analyzed.
Heart (0.39 ppm [b]; Goat No. 1)	Et_2O:TFA	33.3	0.13	Protein (0.18 ppm, 46.2% TRR), triglyceride (0.05 ppm, 12.8% TRR), lactic acid (0.04 ppm, 10.3% TRR), and pyruvic acid (0.02 ppm, 5.1% TRR) were identified in various fractions. Total identified = 0.30 ppm, 77.0% TRR
	MeOH:TFA	18.2	0.07	
	3 N NaOH	30.3	0.12	
	Enzyme	6.1	0.02	
	Non-extractable	6.1	0.02	Not further analyzed.
Muscle (semimembranous) (0.26 ppm [b]; Goat No. 1)	Et_2O:TFA	20.8	0.05	Triglyceride (0.14 ppm, 53.8% TRR), protein (0.10 ppm, 38.5% TRR), lactic acid (0.03 ppm, 11.5% TRR), pyruvic acid (0.03 ppm, 11.5% TRR), and DCA (0.03 ppm) were identified in various fractions. Total identified = 0.33 ppm, 115.3% TRR
	MeOH:TFA	16.7	0.04	
	3 N NaOH	41.7	0.11	
	Enzyme	4.2	0.01	
	Non-extractable	4.2	0.01	Not further analyzed.
Muscle (longissimus dorsi) (0.36 ppm [b]; Goat No. 1)	Et_2O:TFA	38.5	0.14	Triglyceride (0.18 ppm, 50.0% TRR), protein (0.08 ppm, 28.2% TRR), lactic acid (0.04 ppm, 11.1% TRR), and fumaric acid (0.01 ppm, 2.8% TRR) were identified in various fractions. Total identified = 0.34 ppm, 94.4% TRR
	MeOH:TFA	15.4	0.06	
	3 N NaOH	38.5	0.14	
	Enzyme	3.8	0.01	
	Non-extractable	0.0	0.0	
Fat (omental) (1.50 ppm [b]; Goat No. 1)	Et_2O:TFA	82.4	1.24	Triglyceride (1.02 ppm, 68.0% TRR), protein (0.07 ppm, 4.7% TRR), and oleic acid (0.03 ppm, 2.0% TRR) were identified in various fractions. Total identified = 1.12 ppm, 74.7% TRR
	MeOH:TFA	1.5	0.02	
	3 N NaOH	1.5	0.02	
	Enzyme	--	--	
	Non-extractable	--	--	
Fat (back) (1.74 ppm [b]; Goat No. 1)	Et_2O:TFA	100.7	1.75	Triglyceride (1.25 ppm, 71.8% TRR), oleic acid (0.11 ppm, 6.3% TRR), and protein (0.04 ppm, 2.3% TRR) were identified in various fractions. In addition, pyruvic acid, lactic acid, and fumaric acid were identified at ≤0.04 ppm. Total identified = 1.40 ppm, 80.4% TRR
	MeOH:TFA	2.1	0.04	
	3 N NaOH	2.7	0.05	
	Enzyme	--	--	

Table 4. (Continued).

Substrate	Fraction	Malathion equivalents		Characterization/Identification [a]
		% TRR	ppm	
	Non-extractable	--	--	
Fat (perirenal) (1.42 ppm [b]; Goat No. 1)	Et_2O:TFA	70.2	1.00	Triglyceride (0.87 ppm, 61.3% TRR), protein (0.08 ppm, 5.6% TRR), and stearic acid (0.04 ppm, 2.8% TRR) were identified in various fractions. In addition, pyruvic acid, lactic acid, and fumaric acid were identified at $\leq$0.03 ppm.
	MeOH:TFA	1.4	0.02	
	3 N NaOH	2.1	0.03	
	Enzyme	--	--	Total identified = 0.99 ppm, 69.7% TRR
	Non-extractable	12.1	0.17	Not further analyzed.

[a] Data were obtained from registrant's summary tables. The summary data do not specify the metabolites nor the amounts identified per fraction.

[b] TRR values were re-determined prior to characterization/identification of residues.

[c] Identifications were made by a combination of reverse-phase HPLC, anion exchange HPLC, and gel permeation chromatography.

Characterization and identification of residues

The extracts from the second fractionation procedures were analyzed using reverse-phase (C18) HPLC with a Spherisorb ODS-2 column using either one of the following mobile phases: (i) a binary system consisting of 100% water containing 0.2% TFA (Solvent A) changing to 100% acetonitrile containing 0.1% TFA (Solvent B) in a series of step and linear gradients over a period of 50 minutes; or (ii) a ternary system consisting of 100% Solvent A changing to 100% Solvent B in a series of step and linear gradients over a period of 50 minutes, then changing to 100% tetrahydrofuran in a linear gradient over a period of 50 minutes. Metabolites were detected with a UV (230 nm) and a flow-through radioactive monitoring (RAM) detector. The limit of detection was 0.01 ppm. Metabolites were identified by comparison of retention times of unfortified sample extracts with those from the same extract fortified with specific radiolabeled reference standards (desmethyl malathion, diethyl-2-mercaptosuccinate, isomalathion, malaoxon, malathion, malathion dicarboxylic acid, malathion monocarboxylic acid, monoethyl maleate, oleic acid, and stearic acid). TRR values were re-determined in samples of tissues that were used for characterization and identification of residues prior to extraction and characterization/identification; these re-determined TRR values compared favorably with the original TRR values (presented in Table 2).

The polar residues that were not retained by the C18 HPLC system described above were analyzed by anion exchange HPLC on an Aminex HP 87H column using an isocratic mobile phase of 0.01 N sulfuric acid, and UV (210 nm) detection. Eluant fractions were collected and analyzed for radioactivity by LSS. Metabolites were identified by comparison of retention times to reference standards (citric acid, desmethyl malathion, fumaric acid, D-(+)-glucose, lactic acid, malathion, malathion dicarboxylic acid, malathion monocarboxylic acid, malic acid, monoethyl fumarate, monoethyl maleate, pyruvic acid, stearic acid, and succinic acid).

All extracts were additionally analyzed for carbohydrates by gel permeation chromatography (GPC) using with a Waters Sugar-Pac I column with an isocratic mobile phase of water or acetonitrile:water (80:20, v:v), and refractive index detection (RI). Eluant fractions were collected and analyzed for radioactivity by LSS. Metabolites were identified by comparison of retention time to a lactose reference standard.

All milk and tissue samples contained an unknown component having a retention time of ca. 90 minutes when analyzed by reverse-phase HPLC. Additional analytical procedures were conducted to identify the unknown component. To determine whether the component was a fatty acid/triglyceride, an aliquot of the diethyl ether extract of fat (which contained the highest concentration) was saponified with potassium hydroxide in the presence of glycerol at 130 C for 3 hours. After cooling, the mixture was neutralized with sulfuric acid and extracted three times with hexane. The hexane extracts were combined,

evaporated, re-dissolved in tetrahydrofuran, and analyzed by the previously described reverse-phase HPLC. Identification was achieved by comparison to retention times of reference standards (oleic and stearic acid). The aqueous phase remaining after the hexane extraction of fat was directly analyzed by the previously described GPC system. Identification was achieved by comparison to retention times of reference standards (radiolabeled glycerol in blank and fortified samples). To determine whether the unknown component was a tricarboxylic acid (TCA), the methanol extracts obtained from liver and kidney samples were analyzed by the previously described anion exchange HPLC. Identification of metabolites was achieved by comparison to retention times of radiolabeled reference standards (pyruvic, lactic, and fumaric acids in blank and fortified samples).

Additional subsamples of milk were fractionated into fat, whey, and casein and these fractions were investigated for the presence of lactose. The whey was diluted with acetonitrile, filtered, and analyzed using the previously described GPC. Casein was mixed with TRIS buffer (pH 8) or a buffer containing pronase E enzyme and incubated for ca. 16 hours at 37 C. Aliquots were lyophilized, then redissolved in 0.1% TFA, filtered, and analyzed by the previously described reverse-phase HPLC. Identification of metabolites was achieved by comparison to retention times of reference standards (lactose and casein).

Tables 3 and 4 summarize the characterization and identification of ^{14}C-residues in extracts of milk and tissues. The study successfully identified majority of the radioactivity in goat matrices: milk (≥93% TRR), liver (83% TRR), kidney (78% TRR), heart (77% TRR), muscle (≥94% TRR), and fat (≥70% TRR). The principal ^{14}C-residues identified were triglycerides, fatty acids, tricarboxylic acids, lactose, and/or unspecified proteins. The parent malathion was not identified in any matrix. The only immediate malathion metabolites identified were malathion monocarboxylic acid (MCA) and malathion dicarboxylic acid (DCA) which were present in milk, kidney, and muscle in insignificant amounts; see Table 1 for molecular structures. The confirmation of MCA and DCA was accomplished by HPLC analysis using urine samples instead of the substrates where these compounds were tentatively identified; the HPLC retention times of these compounds from urine analysis compared favorably with those from the edible tissues.

The non-extractable residues remaining after hydrolysis procedures were all below the metabolism trigger values, except for perirenal fat. However, no additional characterization/identification will be required on the non-extractable ^{14}C-residues of perirenal fat (0.17 ppm, see Table 4) since the amount is just slightly above the trigger value (0.14 ppm) and ca. 70% of the fat TRR was identified; furthermore, it is unlikely that additional rigorous hydrolysis procedures will result in the identification of immediate malathion metabolites. In general, the analytical method recoveries exceeded 100% of the amount injected into the HPLC, and most of the unidentified radioactivity appeared as numerous HPLC peaks none of which exceeded 0.04 ppm. No additional identifications are required.

Storage stability

The goat matrices that were used for metabolite identification were stored frozen at -10 C for ca. six months prior to analysis. The Agency metabolism guidance document does not require supporting storage stability data when samples are analyzed within 4-6 months of collection, provided evidence is given that attempts were made to limit degradation of residues by appropriate storage of matrices and extracts during the analytical portion of the study.

The present goat metabolism study is supported by acceptable storage stability data.

Radiolabeled validation of analytical methods

Samples from the metabolism study were not analyzed using any of the current enforcement methods. No method validation in meat and milk is required however since no residues of concern were observed in these commodities.

In summary, the qualitative nature of malathion residue in goats is adequately understood. The levels of total radioactive residues in lactating goats administered [2,3-^{14}C]malathion at 115 ppm (1.6x the maximum theoretical dietary dose) in the diet for five consecutive days reached maximums of 2.79 ppm in milk, 2.28 ppm in liver, 2.21 ppm in kidney, 0.39 ppm in heart, 0.36 ppm in muscle, and 1.59 ppm in fat. The study successfully identified the majority ($\geq$70% TRR) of the radioactivity in goat matrices. The principal ^{14}C-residues identified were triglycerides, fatty acids, tricarboxylic acids, lactose, and/or unspecified proteins. The parent malathion was not identified in any matrix. The only immediate malathion metabolites identified were malathion monocarboxylic acid and malathion dicarboxylic acid which were present in milk, kidney, and muscle in insignificant amounts.

Since neither malathion nor malaoxon (the residues of concern) were observed in meat or milk in the subject metabolism study, there is no need for tolerances in these commodities based on any dietary exposure to malathion residues. The present 4 and 0.5 ppm tolerances for malathion in meat and milk respectively involve direct animal treatments which would, in all probability, result in significant malathion residues of concern in these commodities. Therefore, if the direct animal treatment uses of malathion to cattle are canceled, then the present tolerances for meat and milk may be revoked. If the direct livestock treatment use is supported, appropriate dermal metabolism and magnitude of the residue studies are required.

MASTER RECORD IDENTIFICATION NUMBER

Citation for the MRID document referred to in this review are presented below.

42581401 Cannon, J. M., E. Murrill, and V. Reddy (1992) Meat and Milk Metabolism Study in Dairy Goats. Unpublished study conducted by Bio-life Associates, Ltd. (BLAL), Neillsville, WI and Midwest Research Institute (MRI), Kansas City, MO (BLAL Study No. 89 GM 4, MRI Project No. 9660-F) and sponsored by Cheminova Agro A/S. 335 p.